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PATENT & TRADEMARK OFFICE

Attorney Docket No. 5470.220CTXX

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Johnston et al.
Serial No.: 10/683,781
Filing Date: October 10, 2003
For: *Alphavirus RNA Replicon Systems*

Group Art Unit: 1648
Examiner: M. McGaw
Confirmation No.: 2088

Date: October 8, 2004

Mail Stop Interference
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR DECLARATION OF INTERFERENCE

Pursuant to the provisions of 37 C.F.R. §1.608, Applicants respectfully request declaration of an interference between the above-captioned patent application, and U.S. Patent 6,015,694, claims 9-11 thereof. As reflected in the Office Action dated October 22, 2002 in the parent application (USSN 09/620,311), the United States Patent and Trademark Office has assigned claim 9 of U.S. Patent No. 6,015,694 an effective filing date of November 30, 1994.

Applicants submit herewith declarations pursuant to 37 C.F.R. §1.608 including declarations of all of the inventors and corroborating declarations as well as a diligence timeline, which demonstrate possession of the invention in advance of November 30, 1994.

Accordingly, a declaration of interference with U.S. Patent No. 6,015,694 is respectfully requested.

Respectfully submitted,

Karen Magri

Karen A. Magri
Registration No. 41,965

Enclosures:

- Caley Declaration
- Johnston & Davis Declaration (w/ exhibits)
- Lind Declaration
- Lofts Declaration (w/ exhibits)
- Ludwig Declaration (w/ exhibits)
- Parker Declaration (w/ exhibits)
- Pushko Declaration (w/ exhibits)
- Smith Declaration (w/ exhibits)
- Diligence Timeline (w/ exhibits)

CERTIFICATE OF EXPRESS MAILING

"Express Mail" mailing label number: EV472511733US
Date of Deposit: October 8, 2004
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to Mail Stop Interference, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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PATENT & TRADEMARK OFFICE

DOCKET NO. 5470-220CTXX

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: ROBERT E. JOHNSTON, ET AL. ART UNIT:
SERIAL NO.: 10/683,781 EXAMINER
:

FILING DATE: OCTOBER 10, 2003
FOR: ALPHAVIRUS RNA REPLICON SYSTEMS

DECLARATION CATHLEEN LIND, 37 C.F.R. §1.608(b)

ASSISTANT COMMISSIONER FOR PATENTS
PO BOX 1450
ALEXANDRIA, VA 22313-1450

SIR:

I, Cathleen Lind, do hereby declare and state:

1. I am a technician at USAMRIID at Fort Detrick, in Frederick, Maryland. I have a B.S. in Biology from Hood College. I am employed as a scientific research technician in the Virology Division at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID), and my period of employment embraces the time period of November 30, 1994 through May 23, 1995 (hereinafter, "the Activity Time Period") and began well prior to November 30, 1994.

2. During the Activity Time Period, I provided assistance to scientists in the Virology Division of USAMRIID at Fort Detrick in Frederick, Maryland.

3. The support work I performed prior to and during the Activity Time Period occurred predominantly in the V3V4 Virology Laboratory at Fort Detrick, in Building 1425. The V3V4 laboratory is a self-contained and safe environment for conducting virology experiments.

4. I have reviewed the Declarations of Drs. Peter Pushko, Michael Parker, and George V. Ludwig (Pushko, Parker, and Ludwig, respectively, herein) and the detailed record of activity

listed therein.

5. Prior to and during the Activity Time Period, I had the opportunity to observe the research activities detailed in the Declarations of Pushko, Parker, and Ludwig because my duties in the Virology Division at USAMRIID placed me within proximity to Pushko, Parker and Ludwig as they were conducting their research.

6. I observed Pushko's activities and his working space during the time periods detailed in his Declaration and can confirm that I saw activities that are entirely consistent with Pushko's assertions in his Declaration.

7. I observed Parker's activities and his working space during the time periods detailed in his Declaration and can confirm that I saw activities that are entirely consistent with Parker's assertions in his Declaration.

8. I observed Ludwig's activities and his working space during the time periods detailed in his Declaration and can confirm that I saw activities that are entirely consistent with Dr. Ludwig's assertions in his Declaration.

I, Cathleen Lind, declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of U.S. Patent Application Serial No. 10/683,781 or any patent issued thereon.

2 August 04
Date

Cathleen M. Lind
Cathleen Lind

DOCKET NO. 5470-220CTXX

OIPE
OCT 1 2 2004

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: ROBERT E. JOHNSTON, ET AL. ART UNIT:
SERIAL NO.: 10/683,781 EXAMINER
:

FILING DATE: OCTOBER 10, 2003
FOR: ALPHAVIRUS RNA REPLICON SYSTEMS

DECLARATION OF IAN J. CALEY, PH.D., 37 C.F.R. §1.608(b)

ASSISTANT COMMISSIONER FOR PATENTS
PO BOX 1450
ALEXANDRIA, VA 22313-1450

SIR:

I, Ian J. Caley, Ph.D., do hereby declare and state:

1. I have a Ph.D. in Microbiology and Immunology from the University of North Carolina at Chapel Hill (UNC-CH). During the time period of November 30, 1994 through May 23, 1995 (hereinafter, "the Activity Time Period"). I was a graduate student employed as a teaching assistant in the Department of Microbiology and Immunology at the School of Medicine at UNC-CH) where my employment began in August of 1993.

2. Prior to and during the Activity Time Period, I was a graduate student conducting thesis work in the Department of Microbiology and Immunology, under the guidance of Dr. Nancy L. Davis and Dr. Robert E. Johnston (Davis and Johnston, respectively, herein). Johnston was my Ph.D. thesis supervisor. My work at UNC-CH related generally to the development of viral-based vaccines, including vaccines utilizing attenuated Venezuelan equine virus (VEE) sequences under the direction of Davis and Johnston.

3. The experimental work done prior to and during the Activity Time Period occurred predominantly in the Biohazard Level 3 (BL-3) laboratory at UNC-CH, located on the 7th floor of

the Mary Ellen Jones building (formerly known as the Faculty Laboratory Office Building) on the UNC Medical Campus. This was the same laboratory utilized by Davis, Johnston and other members of the Johnston group for VEE-related research.

4. I have reviewed the Declaration of Davis and Johnston.

5. Prior to and during the Activity Time Period, I had the opportunity to observe the activities listed in the Declaration of Davis and Johnston because my duties at UNC-CH placed me within proximity to Davis and Johnston as they were conducting these activities. My own work was conducted in the same laboratory utilized by Davis and Johnston, and predominantly under their direction. Consequently, I had contact with Davis and Johnston on at least a weekly, if not daily, basis.

6. I observed Davis' activities and her working space at UNC-CH during the time periods reported in her declaration and spoke with Davis about her work on a regular basis, as was customary in the lab. I can confirm that I saw activities that are entirely consistent with Davis' assertions in the Declaration of Davis and Johnston.

7. I observed Johnston's activities and his working space during the time period reported in his declaration and can confirm that I saw activity entirely consistent with Johnston's assertions in the Declaration of Davis and Johnston. I was aware that he actively involved in the replicon system project prior to and during the Activity Time Period even though he was not routinely conducting the experiments at the bench.

8. I was also aware that Davis and Johnston were engaged in ongoing collaborations with scientists at the United States Army Medical Research Institute for Infectious Diseases (USAMRIID), in part because I recall that various VEE constructs that I was familiar with in the lab were shipped to scientists at USAMRIID.

I, Ian J. Caley, Ph.D. declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of the U.S. Patent Application Serial No. 10/683,781 or any patent issued thereon.

August 19th, 2004
Date

Ian J. Caley, Ph.D.

DOCKET NO. 5470-220CTXX

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF: ROBERT E. JOHNSTON, ET AL. ART UNIT:
SERIAL NO.: 10/683,781 EXAMINER
:

FILING DATE: OCTOBER 10, 2003
FOR: ALPHAVIRUS RNA REPLICON SYSTEMS

DECLARATION MICHAEL D. PARKER, PH.D., 37 C.F.R. §1.608(b)

ASSISTANT COMMISSIONER FOR PATENTS
PO BOX 1450
ALEXANDRIA, VA 22313-1450

SIR:

I, Michael D. Parker, Ph.D., do hereby declare and state:

1. I am a virologist with a specialization in developing virus-based vaccines. I have a Ph.D. in Microbiology from Colorado State. I am employed as a scientist at the United States Army Medical Research Institute of Infectious Diseases (USAMRIID) where I contributed, through my investigative work, to developing the Alphavirus RNA Replicon Systems of U.S. Patent Application No. 10/683,781. In preparing this declaration I reviewed my original notebooks in addition to other relevant documents. These are cited herein as follows:

Exhibits:

Exhibit A Copy of USAMRIID Notebook #3656 (issued to M. Parker, entries by P. Pushko)

Exhibit D Copy of USAMRIID Notebook #3516, Alphavirus Replicon II, Issued February 23, 1993 (issued to J. Smith, entries by M. Parker)

Exhibit G Memo and ILIR Research Proposal on the Alphavirus RNA Replicon System

Exhibit F Letter from Dr. Nancy Davis, May 24, 1993

Exhibit K Copy of pages 133-152 of USAMRIID Notebook #3354

Exhibit L Copy of USAMRIID Notebook #3354 (entire notebook)

Exhibit M Copy of pages 1-17 of USAMRIID Notebook #3641

Exhibit N Copy of USAMRIID Notebook #3641 (entire notebook)

2. The following is a listing of my laboratory activities related to developing the Alphavirus RNA Replicon Systems of U.S. Patent Application No. 10/683,781 (hereinafter "the '781 application"). My contributions to this project began well in advance of November 30, 1994 and continued through and beyond May 23, 1995.

3. Prior to November 30, 1994 and during the period between November 30, 1994 - May 23, 1995, I conducted research and experimentation as a scientist in the Virology Division of USAMRIID at Fort Detrick in Frederick, Maryland, which is recorded in USAMRIID notebook #3516 (Exhibit D), notebook #3354 (Exhibit L) and notebook #3641 (Exhibit N). Entries in these notebooks were made in my own hand, or on occasion, by colleagues/technicians in the laboratory carrying out my experiments under my direct supervision, all of which would have been discussed with me at the time a given experiment was performed and recorded. As such, I can attest to the substantive accuracy of the aforementioned notebooks.

4. The experimental work reflected in these notebook entries occurred predominantly in the V4 portion of the V3V4 Virology Laboratory at Fort Detrick. The V3V4 laboratory is a self-contained and safe environment for conducting virology experiments.

Activity Record Prior to November 30, 1994

5. Prior to November 30, 1994, I engaged in numerous discussions with Drs. Nancy Davis, Robert Johnston, and Jonathan Smith (Davis, Johnston and Smith, respectively, herein) about how to construct the alphavirus replicons and helper sequences reflected in the '781 application and the assays that would be required to develop and test such constructs. I understand that Davis, Johnston and Smith are designated co-inventors of the subject matter of

the '781 application, and in particular, Claim 116, described below.

6. Prior to November 30, 1994, Jonathan Smith and I prepared a research proposal to fund the development of the Alphavirus RNA Replicon Systems that was to take place at USAMRIID. A copy of the grant proposal, referred to as an "ILIR" was forwarded to the Office of Research Plans and Programs by the Chief of the Virology Division, along with an accompanying cover memo dated August 4, 1993 (Exhibit G). The date stamp in the upper right hand corner indicates the date the ILIR was received by the Office of Research Plans and Programs (i.e., August 9, 1993).

7. I understand that pending Claim 116 of the '781 application reads as follows:

Claim 116. A method of producing an immune response in a subject, comprising:

administering to the subject an effective amount of a composition comprising a population of infectious, defective alphavirus particles in a pharmaceutically acceptable carrier,

wherein each particle comprises one or more heterologous RNA sequence(s) encoding an immunogen; and further wherein the population contains no detectable replication-competent alphavirus particles as determined by passage on permissive cells in culture.

8. The ILIR proposal describes the invention set forth in Claim 116 (Exhibit G, pp. 2-4). The "infectious, defective alphavirus particles" comprising "one or more heterologous RNA sequence(s) encoding an immunogen" is equivalent to the VEE replicon particles encoding the LSN antigen that were produced prior to November 30, 1994. The production of such particles inherently requires the successful development of VEE replicon helper sequences that can produce the requisite structural packaging proteins and a VEE replicon capable of expressing a heterologous RNA sequence encoding an immunogenic protein. The Lassa fever virus nucleoprotein (LSN) was known to be immunogenic if expressed in vivo.

9. Furthermore, the requirement for replicon particles "wherein the population contains

no detectable replication-competent alphavirus particles as determined by passage on permissive cells in culture" generically describes the approach outlined and used to assess the VEE particles. For example, the supernatant of VEE replicon particle-infected cells when incubated with Baby Hamster Kidney (BHK) cells resulted in fewer than 100 plaque forming units per ml of supernatant (pfu/ml), which is the lower limit of detection of the plaque assay. Thus, plaque assays were used to verify that the packaged replicons were "replication defective" or, in other words, incapable of initiating a productive infection.

10. As described in the ILIR (Exhibit G, section 3, pages 3-4), the infectious replication defective replicon particles were intended as a vaccine and administering the particles to animals was an integral part of our original concept.

11. I began developing infectious but replication defective alphavirus replicons well prior to November 30, 1994, which included heterologous RNA sequences encoding various immunogenic proteins. Thus, the required elements for the method of Claim 116 were developed prior to November 30, 1994 when we demonstrated that a VEE replicon particle encoding the LSN antigen was packaged into particles that (1) infected permissive cells, (2) expressed high levels of the LSN antigen, and (3) failed to produce measurable plaques by plaque assay.

12. As documented in my notebook #3516 contains entries from prior to November 30, 1994, which reflect my work on the alphavirus Venezuelan Equine Encephalitis virus or "VEE." replicon system, as is summarized on the index page (Exhibit D, page 1). Periodically and as appropriate, I had technicians and other researchers conduct my experiments and enter the protocols and results in this notebook,

13. I developed VEE replicon sequences that included heterologous RNA encoding antigens of interest with which I had sufficient familiarity such that I knew they would generate

an immune response if expressed at sufficient levels by the VEE replicon. For example, my entries at pages 3 - 7 document the construction of VEE replicons, including those containing the RNA sequence encoding the Lassa fever virus antigen known as the nucleoprotein (Lassa N) and the glycoprotein (Lassa GP, page 129), as are disclosed in the '781 application, in addition to other immunogen encoding sequences. (Exhibit D, #3516, pages 3-12).

14. Page 3 of notebook #3516 also documents that the genomic VEE sequence utilized for constructing some VEE replicons (e.g., "p2-20") was provided by Johnston.

15. Also prior to November 30, 1994, I generated several VEE replicon helpers, as documented, for example, on page 9 of notebook #3516 (Exhibit D; see also pp. 21, 31, 50-52, 74). The structural genes utilized for the helper described on page 9 were derived from the 272.3 clone supplied by Davis and Johnston, which contains attenuating mutations in E2 and E1 gene sequences (see, p. 9).

16. My entries, for example at page 110-111 of #3516 (Exhibit D), document that prior to November 30, 1994, I conducted in vitro transcription assays to confirm that the Lassa N encoding heterologous RNA sequence in a VEE replicon was being expressed in transfected cells and that the Lassa N protein was produced as detected by fluorescent antibody (FA) staining (Exhibit D, pp. 127-128).

17. My notebook #3354 (Exhibit K, pages 133-136 and index page) also documents that I began constructing a replicon helper using the genome of the alphavirus VEE. The genetic material used as the template for this VEE replicon helper was derived from a cDNA clone (referred to as 272-3 in my notebook or v3519 in the '781 application), which was supplied by Davis and Johnston. This VEE clone included three attenuating mutations in VEE structural genes (E2 76 and 209 and E1 253) which were utilized in the replicon helper constructs to prevent the generation of fully virulent replication competent VEE replicon particles in the rare

event of a homologous recombination event between the replicon and the replicon helper (Id.). The entire notebook, #3354, is submitted as Exhibit L.

13. Page 133 of notebook #3354 (Exhibit K) also documents that one general approach to the construction of the replicon helper was to remove as much of the nonstructural (ns) VEE gene sequence as possible.

14. Entries in my laboratory notebooks prior to November 30, 1994 also document my work related to producing infectious replication defective VEE particles wherein each particle included at least one heterologous RNA sequence encoding an immunogenic protein. For example, the index of Notebook #3641 (Alphavirus Replicon Notebook, pp. 1-17, Exhibit M) specifies that several inserts were cloned for inclusion into a replicon (e.g., Ebola virus glycoprotein, CCHF, the C fragment of Botulinum A toxin). My work detailed on page 3 of that notebook documents experimentation used to produce infectious VEE replicon particles containing the sequence encoding Lassa fever virus nucleoprotein ("LSN") antigen discussed in the '781 application and conducted prior to November 30, 1994. These particles were produced using a replicon helper referenced in my notebook as "Help Rsr1."(Exhibit M, #3641, page 3) that I developed prior to November 30, 1994. (My complete notebook #3641 is submitted as Exhibit N).

15. Page 10 of notebook #3641 (Exhibit M) further documents that prior to November 30, 1994, I assayed for the production of Lassa N antigen by Baby Hamster Kidney (BHK) cells infected with VEE replicon particles containing a heterologous RNA sequence encoding the Lassa N antigen (LSN). Detection of the LSN antigen was done using fluorescent labeled antibody ("FA"). Pages 16-17 of the same notebook document similar experiments with the Lassa N containing replicon created with the VEE helper RsrI, including fluorescent antibodies (FA). My notes indicate the LSN antigen was expressed. This result demonstrated that an antigen

could be expressed by a replicon, and therefore, it was expected that the replicon particles would express the antigen in vivo (i.e., when administered to a subject).

16. My entry on page 17 of Notebook #3641 reads "Peter Starts Here!" This comment refers to Peter Pushko (Pushko), who began laboratory work (i.e., experimentation) on the Alphavirus RNA Replicon Systems at USAMRIID prior to November 30, 1994. I understand that Pushko is designated as a co-inventor on the '781 application of the subject matter of Claim 116 discussed above. A laboratory notebook, #3656, that was issued to me on July 8, 1994 was given to Pushko to record his work on the Alphavirus RNA Replicon Systems. The cover of the notebook indicates the subject contained therein is the "VEE Replicon." (Exhibit A, notebook #3656, cover page).

17. My work on the Alphavirus RNA Replicon Systems continued after Pushko's arrival in the lab, as is documented in my notebook #3641 (Exhibit M, pp. 17 - 152).

18. Entries following page 17 of notebook #3641 (Exhibit N) evidence my continuing work on developing additional helper replicon constructs (e.g., Exhibit N, pages 18-20) and cloning of heterologous RNA sequences encoding immunogens of interest (e.g., Exhibit N, pp. 22- 23, 27), VEE replicons carrying these inserts (e.g., Exhibit N, p. 25, Ebola virus NP replicon), and shuttle vectors useful in the construction of VEE replicons and replicon helpers (e.g., Exhibit N, pp. 24, 29).

19. Prior to November 30, 1994 and contemporaneous with my own effort, Davis and Johnston were also constructing VEE replicons and VEE replicon helpers at the University of North Carolina at Chapel Hill. I recall, generally, the discussions with Davis and Johnston directed to the development of VEE-based replicon and helper constructs. Prior to November 30, 1994 our group received samples of some of the VEE replicons (e.g. pVR2) and VEE helper constructs (e.g. v3014) from their lab. Correspondence signed by Davis providing detailed

descriptions of the constructs was sent with the samples to Smith at USAMRIID. A copy of this document was kept on the refrigerator and freezer where these constructs were stored (Exhibit F, letter from Nancy Davis dated May 24, 1993).

I, Michael D. Parker, Ph.D., declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statements may jeopardize the validity of the U.S. Patent Application No. 10/683,781 or any patent issuing therefrom.

08 Sept 04
Date

Michael Parker
Michael D. Parker, Ph.D.